Tetrahedron: *Asymmetry* 21 (2010) 1817–1820

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Diastereo-controlled Diels–Alder cycloadditions of erythrose benzylidene-acetal 1,3-butadienes by 4-substituted-1,2,4-triazoline-3,5-dione: Evidence for the stereoelectronic effects on the dienes

Maria J. Alves *, Vera C. M. Duarte, Hélio Faustino, António Gil Fortes

Departamento de Química, Universidade do Minho, Campus de Gualtar, 4710-057 Braga, Portugal

ARTICLE INFO

Article history:
Received 23 November 2009
Revised 30 April 2010
Accepted 4 May 2010
Available online 30 June 2010

ABSTRACT

Erythrose benzylidene-acetal 1,3-butadienes are studied as partners in Diels–Alder cycloadditions. A high diastereofacial improvement is found in cases where both the alcohol function is protected and a π–π interaction between the diene and dienophile is possible. Several competing factors have been studied independently in order to explain its influence on the selectivity of the cycloadditions.

1. Introduction

Glucosyl-type dienes are excellent partners in Diels–Alder cycloadditions, showing high diastereoselectivity to a range of cyclic or acyclic carba-[1] and aza-[2,3]dienophiles. As part of a project aimed at the synthesis of *C*-aza-disaccharides we looked at the usefulness of 1,3-butadienes bearing an erythrose benzylidene-acetal moiety as a chiral inducer in 4π + 2π cycloadditions. There was a single earlier investigation in this area: dienes of type **1** were combined with 2-methoxycarbonyl-*p*-benzoquinones to build up the AB ring skeleton of Forskolin with high diastereocontrol.[4] Having decided to combine dienes **1** with our target aza-dienophiles, 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) and 4-methyl-1,2,4-triazoline-3,5-dione (MTAD), it became apparent that the cycloaddition selectivities would not be totally controlled in all cases. Based on X-ray structure determinations of the cycloadducts we gained an understanding of the facial selectivity of dienes **1**.

2. Synthesis of 1,3-butadienes 1a–d

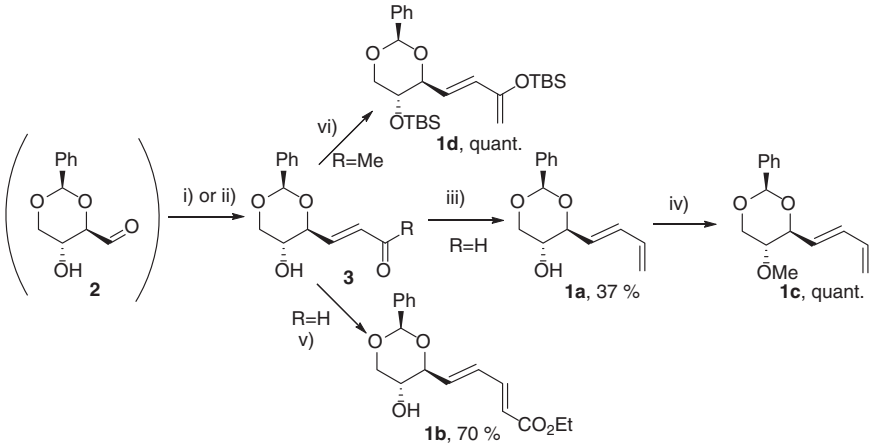
1,3-Butadienes **1a–c** were easily prepared from the aldehyde **2**, which was available in a two-step procedure from D-glucose.[5,6] Butadiene **1a** was obtained from **2** by a double Wittig reaction, in a one-pot procedure, by adding successively $Ph_3PCHCHO$ (1.1 equiv) under anhydrous PTSA catalysis in dry THF followed by Ph_3PCH_3Br and ^{t}BuLi. The enal intermediate **3** (R = H) was isolated as a single isomer, its configuration around C-1′/C-2′ was assigned as *trans*, according to H-1′–H-2′ coupling constant ($J_{1',2'}$ = 15.8 Hz). Butadiene **1b** was analogously prepared from **3**, by choosing the $Bu_3P{=}CHCO_2Et$ reagent in the second step. Compound **1c** was obtained from **1a** by methylation of the hydroxyl group with MeI in the presence of NaH. Compound **1d** was also obtained from aldehyde **2**, by the intermediacy of ketone **3**[7] (R = Me) that was isolated and then converted into **1d** by addition of TBSOTf (2.2 equiv) in the presence of TEA (2.2 equiv) in quantitative yield (Scheme 1). The literature preparation of **1a** requires a non-environmentally friendly synthesis by an oxymercuration–demercuration method.[4,8] Diene **1c** had been obtained previously by methylation from **1a**.[4] The other dienes **1b** and **1d** are, to the best of our knowledge, new compounds and were fully characterized. The typical *trans* coupling constant, $J_{1',2'}$, was verified in every case: diene **1a** showed J = 14.8 Hz; diene **1b** J = 15.3 Hz and so diene **1c** J = 14.6 Hz and diene **1d** J = 15.4 Hz.

3. Cycloadditions of dienes 1a–d to PTAD and MTAD

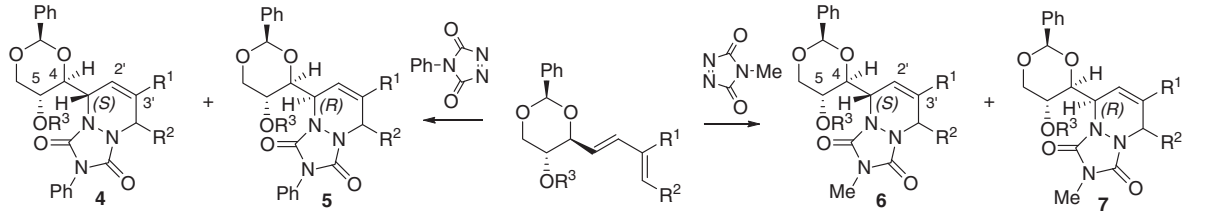
PTAD reacted at −78 °C with the four dienes in dichloromethane. Products consisted of mixtures of diastereomers **4** and **5** when the alcohol function was unprotected, or diastereomerically pure compounds **4** when the alcohol function was protected (Scheme 2). MTDA (4-methyl-3*H*-1,2,4-triazole-3,5(4*H*)-dione) was used in reactions with dienes **1a** and **1c** keeping the reaction conditions observed before with PTAD. Products consisted of mixtures of diastereomers **6a** and **7a** in 2:1 isomeric ratio, when the alcohol function was unprotected, or in 4.5:1 ratio when the alcohol function was protected with a methyl group giving **6a**/**7c** (Scheme 2). The closer ratio of isomers in reaction of diene **1a** with MTAD compared with the reaction with PTAD can be accounted for by the π–π interaction between the diene **1a** with PTAD in the transition state. The better ratio of isomers in the reaction of diene **1c** with MTAD (4.5:1) compared with reaction of **1a** with MTAD shows the importance of the stereoelectronic effect of the alcohol protection group. Both reactions of dienes **1a** and **1c** with MTAD demonstrated that the charge transfer between phenyl groups is important in Diels–Alder reactions of erythrose dienes with PTAD,

* Corresponding author. Tel.: +351253604376.
E-mail address: mja@quimica.uminho.pt (M.J. Alves).

0957-4166/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2010.05.001



Scheme 1.



isomers	d.r.	yield
4a: 5a	5:1	(66 % + 16 %)[a]
4b: 5b	1.6:1	(27 % + 17 %)[a]
4c	----	67 %
4d	----	61 %

a) both isomers were isolated

isomers	d.r.	yield
6a: 7a	2:1	(41 % + 32 %)[a]
6c: 7c	4.5:1	(53 %)[b)c)]

a) both isomers were isolated;
b) total yield of both isomers after chromatography 73%
c) isolated isomer **6c** (53%)

Scheme 2.

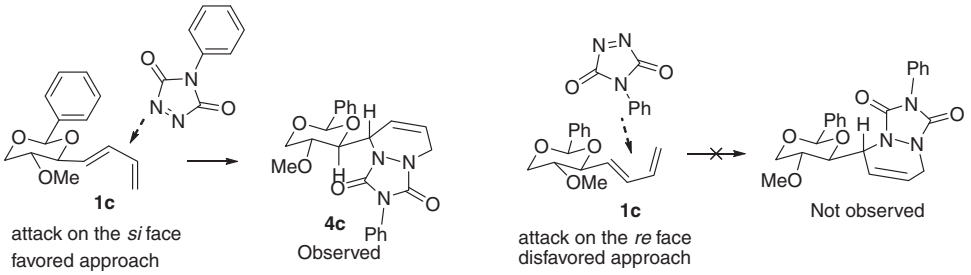


Figure 1.

since the isomeric ratio is substantially diminished in reactions performed with MTAD. The results are summarized in Scheme 2.

To further rationalize the facial discrimination of the cycloaddition process we devised an experiment to test a possible hydrogen-bonding coordination between the hydroxy group of the diene and any of the polar atoms/groups in the dienophile. Such intermolecular hydrogen-bonding has been described to influence the outcome of the selectivity, both in Diels–Alder[9,10] and in dipolar cycloadditions.[11] The solvation of the hydroxy group by DMF is expected to interrupt the possible intermolecular hydrogen-bonding in the approaching reagents. Diene **1a** was reacted with PTAD at −78 °C in dry DMF to determine any ratio difference of isomers **4a**:**5a**. The same 5:1 ratio of isomers **4a**:**5a** was obtained as previously described in dichloromethane. Clearly, no hydrogen-bonding with the naked hydroxy group in compound **1a** is responsible for favoring the attack on the *re* face in cases **c** and **d** (see Fig. 1).

According to ChemBio 3D software a 180° dihedral angle is to be expected for H-1′–C1′–C-4–H-4 moiety of the molecule, both in (*R*)- and (*S*)-configurations. ^{1}H NMR spectra, however, show in some cases an *anti* disposition of H-1′–H-4 and in other cases the *syn* conformation is preferred. Comparison of ^{1}H NMR coupling constants between H-1 and H-4 for adducts showed values between 9.3 and 9.8 Hz in both **4b**, **5b** and **4d** (related to the *anti* disposition) and in both **4a**, **5a** and in **4c** (related to the *syn* disposition). The lack of consistency between the examples observed clearly means a very narrow energy gap between the *anti* and *syn* conformers. X-ray analysis, therefore, becomes the only tool to solve the absolute configuration at C-1′.

Fortunately, compound **4c** could be crystallized and its structure determined by X-ray crystallography; C-1′ was found to have the (*S*)-configuration. Also **4a**, the major component of the mixture **4a** and **5a**, was crystallized and the stereochemistry was found to

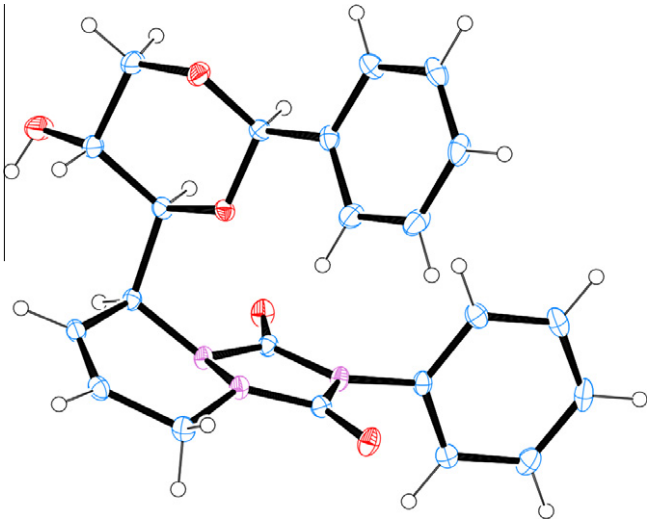


Figure 2. ORTEP view of the molecular structure of the compound **4a**.

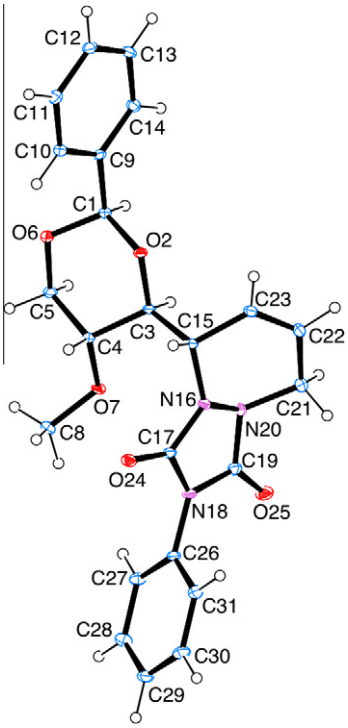


Figure 3. ORTEP view of the molecular structure of the compound **4c**.

be the same. Curiously, the X-ray of compound **4c** exhibits the opposite conformation (*anti*) to that observed in $CDCl_3$ solution (*syn*). Compound **6a** showed to be (*S*)-configuration with an *anti* disposition of H1′–H4.

Most predictably, the bulky substituents on the six-membered acetal ring would prefer to occupy equatorial positions. Two ground state conformers of diene **1c** are represented in Figure 1. These two conformers direct PTAD with a different angle of attack. In the upper conformer PTAD attacks the rear face (*si*) leading to the observed (*S*)-configuration at C-1′. In the lower conformer PTAD accesses the rear face (*re*) of the diene leading to the not observed (*R*)-configuration. Figure 1 shows how a protecting group on the alcohol function at C-5 is able to cause a stereoblocking effect on the front faces of either conformers and how electronic

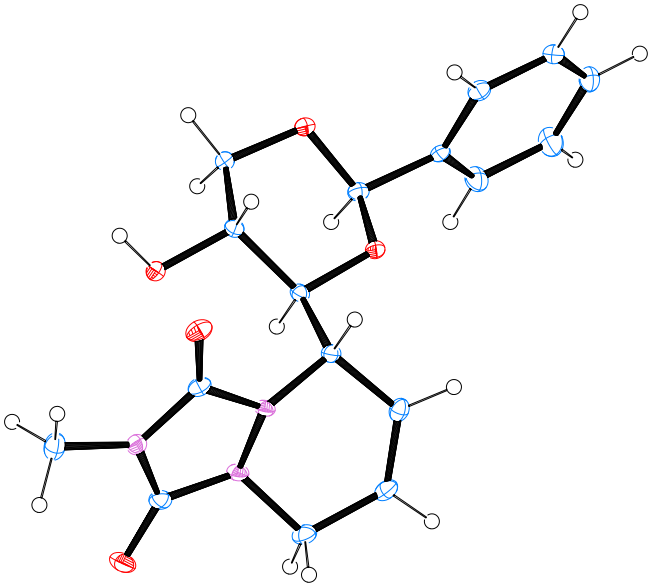


Figure 4. ORTEP view of the molecular structure of the compound **6a**.

charge transfer can happen between the two phenyl groups of reagents on the left side of Figure 1.

Of course the observed structure **4** obtained by X-ray proves neither an *endo* or an *exo* approach; the easy inversion of the nitrogen bridge atom configuration makes such a distinction not possible. The *endo* approach of reagents is suggested on the basis of the stereochemistry of the adducts in the cases of 2-methoxycarbonyl-*p*-benzoquinones with dienes of type **1** previously reported,[4] and by the fact that *endo* approaches had been suggested for PTAD to other glucosyl-bond dienes.[1,2] X-ray structures of compounds **4a** and **4c** are presented in Figures 2 and 3. X-ray structure of compound **6a** is represented in Figure 4.

Assignments of isomers **4** and **5** were based on ^{1}H NMR spectroscopic analysis. Chemical shifts and coupling constants of the hydrogens on the tetrahydropyridazine ring of these compounds were based on H-1′ and H-4′ that show up in the aliphatic region; H-1′ shows at a lower field (δ_H = 5.0–5.2 ppm) due to the combined effects of the nitrogen atom and the vinyl moiety. The two H-4′ in compounds **4a**, **c** are ddd signals with a large geminal coupling ($J \approx 16.5$ Hz) and two small J vicinal and long range-couplings constants ($J \approx 5.0$ Hz and $J \approx 2.0$ Hz). The vinyl protons H-2′ and H-3′ appeared as multiplets at the typical vinylic region δ_H = 6.0–6.3 ppm. The main differences between isomers **4** and **5** are the higher δ_H ca. 0.1 ppm for H-1′ in isomer **5** compared to **4**. Compounds **4b** and **5b** were differentiated only on the basis of the chemical shift difference between the two H-1′. Also compound from case **d**, which was not possible to crystallize display H-1′ consistent with structure **4** (Scheme 1). Compound **6a** was identified by X-ray, with an H-1′ chemical shift about 0.04 ppm higher than that of **7a**. Also the same kind of H-1′ difference was obtained for adducts **6c** and **7c**. ^{13}C NMR spectra are consistent with the assigned structures for compounds **4–7**.

4. Conclusion

An analysis of the stereofactors influencing the selectivity of the Diels–Alder cycloaddition between PTAD and dienes **1a–d** was investigated by performing a designed set of experiments. It was demonstrated how different factors control the stereoelectronic effect. We expect that this knowledge could be further applied to other dienophiles aiding to the synthesis of interesting molecules.

Acknowledgments

We thank FCT for project funding PTDC/QUI/67407/2006; FCT and FEDER for funding NMR spectrometer Bruker Avance II 400 as part of the National NMR Network. We thank Daniela Salgueiro for having preparing some precursors and Dr Thomas Gilchrist for reading the manuscript.

References

1. Larsen, D. S.; Stoodley, R. J. *J. Chem. Soc., Perkin Trans. I* **1989**, 1841–1852.
2. Aspinall, I. H.; Cowley, P. M.; Stoodley, R. J. *Tetrahedron Lett.* **1994**, 3397–3400.
3. Aspinall, I. H.; Cowley, P. M.; Mitchell, G.; Stoodley, R. J. *J. Chem. Soc., Chem. Commun.* **1993**, 1179–1180.
4. Mukhopadhyay, A.; Ali, S. M.; Husain, M.; Suryawanshi, S. N.; Bhakuni, D. S. *Tetrahedron Lett.* **1989**, *30*, 1853–1856.
5. Baker, S. R.; Clissold, D. W.; McKillop, A. *Tetrahedron Lett.* **1988**, *29*, 991–994.
6. Zimmermann, P.; Schmidt, R. R. *Liebigs Ann. Chem.* **1988**, 663–667.
7. Ruijter, E.; Schltingkemper, H.; Wessjohann, L. A. *J. Org. Chem.* **2005**, *70*, 2820–2823.
8. Mukhopadhyay, A.; Suryawanshi, S. N.; Bhakuni, D. S. *Indian J. Chem., Sect B* **1988**, *27B*, 1009–1011.
9. Trost, B. M.; Lee, D. C. *J. Org. Chem.* **1989**, *54*, 2271–2274.
10. Tripathy, R.; Carroll, P. J.; Thornton, E. R. *J. Am. Chem. Soc.* **1991**, *113*, 7630–7640.
11. Houk, K. N.; Moses, S. R.; Wu, Y.-D.; Rondan, N. G.; Jager, V.; Schohe, R.; Fronczek, F. R. *J. Am. Chem. Soc.* **1984**, *106*, 3880–3882.